

# **Nodules in the Cirrhotic Liver**

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Cirrhosis is a common liver disease that is becoming even more prevalent due to the rapid worldwide increase in the incidence of hepatitis C. One of the most important complications of cirrhosis is the development of hepatocellular carcinoma (HCC). Unlike many other malignancies, HCC has a low rate of metastasis when detected early, when it is well circumscribed and 5 cm or less. Additionally, local ablative treatment of HCC using radiofrequency ablation or other methods is highly effective. Successful ablation of an early HCC in a patient with viral hepatitis should not be considered curative however; the remaining liver parenchyma is premalignant, so hepatic transplantation is presently the most successful method for long term cure and prevention of malignancy. In contrast, there is currently no effective treatment for HCC once it has spread beyond the liver. Detection of HCC when it is small and encapsulated has the potential for great improvement in outcome for patients with cirrhosis. In practice, however, imaging has had suboptimal sensitivity for detecting small HCC, and frequent false positive imaging results further reduce its benefit for routine imaging of patients at risk for HCC. In this presentation, we will compare the imaging features of small HCC with those of benign entities that may mimic HCC. A practical approach for interpreting and reporting MRI exams will be discussed that takes into account the impact of the false negative and false positive findings, as well as the risk status of these patients and the natural history of early HCC.

## **HCC vs. benign pseudolesion**

Early HCC is often hyperintense or isointense on T1-weighted images, and is frequently surrounded by a fibrous capsule. HCC is commonly subtle on T2 weighted images (1). Although early grade I HCCs retain substantial portal venous perfusion (2), most detected HCCs are hypervascular. Dynamic imaging after bolus injection of contrast agents is therefore particularly important for detection of HCC (3-6). The typical pattern of enhancement of HCC includes rapid homogeneous enhancement, causing hyperintensity on arterial phase images. This is usually followed by isointensity or hypointensity on portal venous phase images, as the rest of the liver enhances. Most often, HCC is hypointense on delayed, extracellular phase images (7), due to the abundant interstitial space in cirrhotic liver parenchyma. In fact, early non-hypervascular HCCs are sometimes depicted best on delayed phase images. If present, a capsule surrounding HCC enhances little on arterial phase images but becomes progressively hyperintense on later images, typical of fibrous tissue.

Subcentimeter lesions seen only on arterial phase images are extremely common in cirrhotic livers, but approximately 90% are benign (8). Recent work with single breathhold multi-phase arterial phase dynamic imaging indicates increased specificity for distinguishing hepatocellular carcinoma from hypervascular pseudolesions (9-11). Compared with hypervascular pseudolesions, enhancement of HCC typically occurs earlier, persists for a shorter duration, and shows a distinctive transient corona-like spread. Most benign hypervascular pseudolesions are foci of arteriportal shunting or other

causes of reduced portal venous perfusion, accompanied by compensatory increased arterial perfusion. Another less well-documented hypervascular benign nodule, of uncertain incidence, is hyperplastic nodule.

### **Hyperplastic nodule**

Hyperplastic nodules, with histological and etiologic similarity to focal nodular hyperplasia (FNH)(12-15), occur commonly with chronic Budd-Chiari syndrome and occasionally in cirrhotic livers. FNH and other hyperplastic nodules are thought to arise from a hyperplastic response to locally deficient portal venous perfusion, giving rise to benign liver tissue that is perfused entirely by hepatic arteries. Although portal venous remnants may be present histologically, there is generally no intact connection with the portal venous system, and venous drainage is entirely into hepatic venules. Multiple hyperplastic nodules in livers with impaired portal venous perfusion are often referred to as nodular regenerative hyperplasia.

The term “focal nodular hyperplasia” is generally reserved for hyperplastic lesions that occur within otherwise normal liver parenchyma, while the more generic term “hyperplastic nodule” can be applied to similar nodules that occur in livers with impaired portal venous perfusion, such as in Budd-Chiari syndrome, cirrhosis, or in patient with chronic portal thrombosis or larger porto-systemic fistula. These lesions are sometimes referred to as “FNH-like nodule” which, when spelled out, is “focal nodular hyperplasia like nodule”. We prefer the less redundant descriptive term “hyperplastic nodule”.

Unfortunately, much of the literature is unclear regarding the nature of hyperplastic nodules, principally because these nodules in cirrhotic liver resemble regenerative nodules. Most literature based on pathologic classification is concerned principally with distinguishing between benign, dysplastic and neoplastic lesions, including the important document “Terminology of nodular hepatocellular lesions. International Working Party”. (16) The lack of portal venous supply, and intense enhancement during the arterial phase following bolus injection of contrast material, is obvious by imaging but not visibly microscopically.

### **Regenerative and Dysplastic Nodule**

Regenerative nodules are composed of benign liver tissue, closer to normal parenchyma than the fibrotic septations separating them. Regenerative nodules have MRI characteristics identical to those of normal liver, although the scarred and inflamed tissue in the remainder of the liver may have higher signal intensity on T1-weighted images and lower signal intensity on T2-weighted images.

Dysplastic nodules are intermediate pre-malignant lesions that share features with both regenerative nodules and HCC. These nodules are typically hyperintense to isointense on T1-weighted images, and hypointense to isointense on T2-weighted images. Dysplastic nodules are virtually never hyperintense on T2-weighted images; hyperintensity on T2-weighted images is therefore one of the most reliable signs in distinguishing small HCCs from dysplastic nodules. However, many HCCs are not hyperintense. Dysplastic nodules usually enhance maximally on portal phase images, similar to background cirrhotic liver, but early enhancement identical to that of HCC can occasionally be seen. The changes in vascularity from benign to dysplastic to neoplastic involve transition from normal paired hepatic arterial and portal venous perfusion, to

abnormal unpaired arterial perfusion resulting from angiogenesis. The transition can be gradual, giving rise to variable perfusion of dysplastic nodule and HCC, and inevitable overlap in appearances between HCC and advanced dysplastic nodules.

A stepwise pattern of carcinogenesis, from regenerative to larger regenerative to dysplastic to high-grade dysplastic to malignant nodule has been described. This does not mean that a given nodule converts entirely along this pathway. Rather, focal cellular dedifferentiation occurs, with more rapid growth of higher grade dysplasia compared with surrounding benign regeneration, and eventually with a small focus of HCC obliterating the remnants of the preexisting benign and low grade portions. In some cases, small HCC can be seen within a large dysplastic nodule, causing a nodule-within-nodule appearance (17, 18). Therefore, a nodule containing one or more internal nodules, or a mosaic appearance, is a strong sign of HCC; dysplastic nodules should always have simple internal morphology and simple round shape, unless there has been malignant dedifferentiation. The nodule-in-nodule appearance, however, is uncommon. More typically, early HCC is seen without identifiable remnants of a preexisting dysplastic nodule; possibly, the HCC arose within a small dysplastic nodule.

### **Risk-based reporting of small rapid enhancing foci**

The most common problem and source of confusion in the clinical practice of imaging and reporting focal findings in cirrhotic livers results from identification of small “UBOs” (unidentified bright objects). This will remain difficult for the foreseeable future, but the following principles provide a framework for approaching this task.

1. The patient with cirrhosis, especially from viral hepatitis, is at high risk for developing HCC, even if no lesion is seen. HCC smaller than 1 cm is commonly not visible, and new HCC may arise.

2. Subcentimeter foci of rapid enhancement, not visible on any other images, are usually benign.

3. Based on #s 1 & 2 above, the nearly ubiquitous observation of subcentimeter foci of transient enhancement does not change in any measurably way the risk status of the patient. These patients should continue to be imaged at regular intervals to detect HCC.

4. HCC rarely metastasizes outside the liver when less than 3 cm. Therefore, a false negative report of subcentimeter HCC is unlikely to result in untreatable HCC if the patient continues to be imaged at regular intervals.

### **Categories of suspicion for HCC:**

1. “No lesion with high suspicion of HCC”. There may be subcentimeter foci of transient enhancement, but none of these are visible on any unenhanced or later-phase enhanced images. However, HCC can never be excluded with certainty in a cirrhotic liver using existing techniques, so serial MRI is recommended by some investigators (6, 19). Most of these patients at our institution have serial MRI at 12-month intervals, but the most cost-effective interval for regular surveillance has not been determined.

2. “Indeterminate nodule”. These may be nodules greater than one cm that either show rapid enhancement or have high signal intensity on T1-weighted images. Depending on the size and level of suspicion, imaging may be repeated in 3 or 6 months. Repeat imaging at 3 months or less, or biopsy, may be recommended if a lesion is 2 cm or larger, because a doubling of its size is more problematic.

3. “Probable HCC”. These may be followed at 6 weeks, biopsied, or treated, depending on other aspects of a patient’s clinical status. If a lesion is hypervascular, the initial treatment is usual chemoembolization, sometimes followed by radiofrequency ablation (RFA), whereas nonhypervascular HCC is usually treated initially by RFA.

4. “HCC”. When findings are sufficiently characteristic, we consider MRI diagnostic, and do not recommend biopsy or follow-up. These lesions are treated, either by ablation or liver transplantation. HCC greater than 2 cm is considered an indication for increased priority for liver transplantation, with “tumor point” added to the patient’s MELD score. HCC larger than 5 cm, or larger than 3 cm if more than one is present, are currently considered contraindication to liver transplantation.

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